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CHRISTENSEN, O'CONNOR, JOHNSON, KINDNESS, PLLC
1420 FIFTH AVENUE
SUITE 2800
SEATTLE, WA 98101-2347

EXAMINER	
BRUSCA, JOEIN S	

ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
05/12/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

efiling@cojk.com

Office Action Summary	Application No.	Applicant(s)	
	10/523,143	SCHADT ET AL.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23-25,28-30,33,35-37,40-50,52-54,107,252,253 and 258-262* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21, 23-25, 28-30, 33, 35-37, 40-50, 52-54, 107, 252, 253, and 258-262* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-21, 23-25, 28-30, 33, 35-37, 40-50, 52-54, 107, 252, 253, and 258-262 are pending.

2. Claims 1-21, 23-25, 28-30, 33, 35-37, 40-50, 52-54, 107, 252, 253, and 258-262 are rejected.

Continued Examination Under 37 CFR 1.114

3. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 30 April 2010 has been entered.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 259-261 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 259-261 are indefinite because all variables in the claims are not defined, nor is there a limiting definition for such variables in the specification. This indefiniteness precludes rejection under 35 102 or 103 until the meaning of all variables are made clear.

6. Applicant's arguments filed 30 April 2010 have been fully considered but they are not persuasive. The amendment to the claims filed 30 April 2010 defines the variable γ but does not adequately define the meaning of the variables ε and σ regarding how they relate to the particulars of the claimed subject matter.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 2, 5-11, 42-44, 49, 50, 52, 53, 252, and 258 are rejected under 35 U.S.C. 102(b) as being anticipated by Aitman et al. (cited as reference C01 in the Information Disclosure Statement filed 06 March 2006, Nature Genetics Vol. 21, pages 76-83 (1999)).

The claims are drawn to a method of measuring an expression quantitative trait locus (eQTL), a clinical quantitative trait locus (cQTL), and determining whether the gene assayed in the determination of the eQTL and the clinical trait are associated by determining if the eQTL and cQTL map to the same locus. The eQTL is limited to be an expression statistic for the gene that is the trait, i.e. the eQTL is a cis eQTL as limited in the claimed subject matter and discussed on page 95 of the specification. In some embodiments the eQTL and cQTL are the same pleiotropic QTL, the analysis uses genetic maps reflecting the genotype of an individual, the analysis uses restriction fragment length polymorphisms, the analysis uses pedigree data and F2 populations, the trait is a complex trait with incomplete penetrance, some individuals do not have

an allele that predisposes to a disease trait, the complex trait is diabetes, the eQTL and cQTL are colocalized within 6 centimorgans (cM), genetic linkage is observed between the eQTL and the cQTL, and the eQTL and the cQTL are shown to be a common QTL and are not merely in linkage disequilibrium (i.e., closely linked).

Aitman et al. shows in the abstract a method of genetically analyzing complex disorders such as diabetes by correlating a QTL for different traits of diabetes (insulin-mediated glucose uptake and catecholamine-mediated lipolysis) with mapping of the expression trait for the gene Cd36. Aitman et al. used spontaneously hypertensive rat (SHR) animals as the phenotype that was mapped by both eQTL and cQTL. Aitman et al. maps insulin-mediated glucose uptake and catecholamine-mediated lipolysis to a region near the microsatellite marker D4Bro1 on pages 76-77, which is a determination of a cQTL. Aitman et al. employs F2 crossed rats to map insulin-mediated glucose uptake and catecholamine-mediated lipolysis on page 79 to Cd36, which is a refinement of the mapping of the cQTL. Aitman et al. shows in figure 2 and the discussion on pages 77-78 analysis of expression level microarrays determined that expression of Cd36 correlates with SHR individuals relative to SHR.4 and BN individuals. Cd36 was then mapped to a region near the D4Bro1 site in figures 3 and page 78 using radiation hybrids to a precision of about 1cM with a Lod of 5.1 to 9.6 for the intervals measured. The mapping used a plurality of rat/hamster radiation hybrid cell lines to test a plurality of chromosomal locations for linkage to Cd36. Aitman et al. refined the mapping of Cd36 by use of linkage analysis on page 78 and figure 7 by testing linkage to chromosomal DNA of three rat strains. Page 79 and figure 7 show that Cd36 mutations correlate with the trait and that a normal and an affected strain differ by a

duplication or deletion of the Cd36 gene. Figure 1 and column 1 on page 77 show that the phenotype in affected individuals has partial penetrance in affecting glucose uptake.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1 and 12-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aitman et al.

The claims are drawn to a method of measuring an expression quantitative trait locus (eQTL), a clinical quantitative trait locus (cQTL), and determining whether the gene assayed in the determination of the eQTL and the clinical trait are associated by determining if the eQTL and cQTL map to the same locus. The eQTL is limited to be an expression statistic for the gene

that is the trait, i.e. the eQTL is a cis eQTL as limited in the claimed subject matter and discussed on page 95 of the specification. In some embodiments the eQTL is determined from a normalized expression value, the expression level is determined by measurement of an mRNA by use of a microarray, and the normalization is done by either a normalization gene set, a ratio median correction, or a background correction.

Aitman et al. shows in the abstract a method of genetically analyzing complex disorders such as diabetes by correlating a QTL for different traits of diabetes (insulin-mediated glucose uptake and catecholamine-mediated lipolysis) with mapping of the expression trait for the gene Cd36. Aitman et al. used spontaneously hypertensive rat (SHR) animals as the phenotype that was mapped by both eQTL and cQTL. Aitman et al. maps insulin-mediated glucose uptake and catecholamine-mediated lipolysis to a region near the microsatellite marker D4Bro1 on pages 76-77, which is a determination of a cQTL. Aitman et al. employs F2 crossed rats to map insulin-mediated glucose uptake and catecholamine-mediated lipolysis on page 79 to Cd36, which is a refinement of the mapping of the cQTL. Aitman et al. shows in figure 2 and the discussion on pages 77-78 analysis of expression level microarrays determined that expression of Cd36 correlates with SHR individuals relative to SHR.4 and BN individuals. Cd36 was then mapped to a region near the D4Bro1 site in figures 3 and page 78 using radiation hybrids to a precision of about 1cM with a Lod of 5.1 to 9.6 for the intervals measured. The mapping used a plurality of rat/hamster radiation hybrid cell lines to test a plurality of chromosomal locations for linkage to Cd36. Aitman et al. refined the mapping of Cd36 by use of linkage analysis on page 78 and figure 7 by testing linkage to chromosomal DNA of three rat strains. Page 79 and figure 7 show that Cd36 mutations correlate with the trait and that a normal and an affected strain differ by a

duplication or deletion of the Cd36 gene. Figure 1 and column 1 on page 77 show that the phenotype in affected individuals has partial penetrance in affecting glucose uptake. Figure 1 and column 1 on page 77 show that the phenotype in affected individuals has partial penetrance in affecting glucose uptake. Aitman et al. shows in the legend to figure 2 and the methods section on page 82 that the sample applied to the microarray was made from mRNA. Aitman et al. shows on page 82 that the microarray comprises control probes for housekeeping genes, and synthetic, yeast, and human probes that would not be expected to hybridize the rat cDNA samples. Two differently fluorophore labeled samples from different rat strains were simultaneously applied to the microarray, and the ratios of hybridization were determined for each probe on the microarray.

Aitman et al. does not discuss how the raw data of the microarray was processed to give the final expression ratios reported on page77.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to process the raw data of the microarray of Aitman et al. by subtracting background hybridization levels by use of the non-homologous probe signal levels included in the microarray as controls, and it would be further obvious to convert the levels of each measured fluorophore for each probe as a ratio of signals rather than two raw signals because Aitman et al. is interested in determining the relative levels of expression of every measured gene in the two compared strains, as reported on page 77 of Aitman et al.

11. Claims 1, 3, 4, 17-21, 23-25, 28-30, 33, 35-37, 40, 41, and 45-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aitman et al. in view of Dominiczak et al. (Hypertension Vol. 35 (part 2), pages 164-172 (2000))

The claims are drawn to a method of measuring an expression quantitative trait locus (eQTL), a clinical quantitative trait locus (cQTL), and determining whether the gene assayed in the determination of the eQTL and the clinical trait are associated by determining if the eQTL and cQTL map to the same locus. The eQTL is limited to be an expression statistic for the gene that is the trait, i.e. the eQTL is a cis eQTL as limited in the claimed subject matter and discussed on page 95 of the specification. In some embodiments the eQTL and cQTL are colocalized within 1 centimorgan (cM). In some embodiments either the eQTL linkage or the cQTL linkage is tested at a plurality of positions in the genome with a precision of at least 2.5 cM, and a statistical score for the linkage is determined that is a Lod score of greater than 5.0. In some embodiments the individual is a human. In some embodiments the complex trait is the effect of a mutation in a plurality of genes, the complex has a high frequency of disease causing alleles, the trait does not exhibit Mendelian inheritance, or the trait is hypertension.

Aitman et al. shows in the abstract a method of genetically analyzing complex disorders such as diabetes by correlating a QTL for different traits of diabetes (insulin-mediated glucose uptake and catecholamine-mediated lipolysis) with mapping of the expression trait for the gene Cd36. Aitman et al. used spontaneously hypertensive rat (SHR) animals as the phenotype that was mapped by both eQTL and cQTL. Aitman et al. maps insulin-mediated glucose uptake and catecholamine-mediated lipolysis to a region near the microsatellite marker D4Bro1 on pages 76-77, which is a determination of a cQTL. Aitman et al. employs F2 crossed rats to map insulin-mediated glucose uptake and catecholamine-mediated lipolysis on page 79 to Cd36, which is a refinement of the mapping of the cQTL. Aitman et al. shows in figure 2 and the discussion on pages 77-78 analysis of expression level microarrays determined that expression of Cd36

correlates with SHR individuals relative to SHR.4 and BN individuals. Cd36 was then mapped to a region near the D4Bro1 site in figures 3 and page 78 using radiation hybrids to a precision of about 1cM with a Lod of 5.1 to 9.6 for the intervals measured. The mapping used a plurality of rat/hamster radiation hybrid cell lines to test a plurality of chromosomal locations for linkage to Cd36. Aitman et al. refined the mapping of Cd36 by use of linkage analysis on page 78 and figure 7 by testing linkage to chromosomal DNA of three rat strains. Page 79 and figure 7 show that Cd36 mutations correlate with the trait and that a normal and an affected strain differ by a duplication or deletion of the Cd36 gene. Figure 1 and column 1 on page 77 show that the phenotype in affected individuals has partial penetrance in affecting glucose uptake. Figure 1 and column 1 on page 77 show that the phenotype in affected individuals has partial penetrance in affecting glucose uptake. Aitman et al. shows use of congenic rats to map QTL with higher precision than that achieved by F2 analysis.

Aitman et al. does not show mapping of a QTL with a precision of 1 cM, or show an eQTL that maps to a plurality of positions in a genome. Aitman et al. does not show analysis of a human QTL. Aitman et al. does not show analysis of a trait affected by a plurality of mutations in different genes, or a high frequency of disease causing alleles, or non-Mendelian inheritance (limited penetrance) of a trait, or a trait that is hypertension.

Dominiczak et al. reviews the genetics of hypertension. Dominiczak et al. shows on the first column of page 165 that human genes have been identified that contribute to hypertension (a quantitative trait) with a Lod score of greater than 2. Table 1 shows rat loci and alleles that confer hypertension in strains that contain the allele. The alleles are on different chromosomes, and contribute to hypertension with Lod scores ranging from 3.0 to 16.6. Dominiczak et al. notes

the work of Aitman et al. on page 167 as being an important advance in genetic analysis of disease traits. Dominiczak et al. shows on pages 167 through 169 the use of congenic strains to map a QTL. Dominiczak et al. shows on page 169 that more refined mapping to a precision of 1 cM is desirable for positional cloning of desired loci, which requires substitution mapping and knowledge of high density polymorphic markers.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the analysis of Aitman et al. by analyzing human QTL markers, and to more precisely map the analyzed QTL markers, and to extend the analysis to a plurality of QTL markers with limited penetrance because Dominiczak et al. shows that hypertension is caused by a plurality of limited penetrance alleles at different loci. It would have been further obvious to map the QTL markers with higher precision because Dominiczak et al. state that such precision allows for positional cloning of the markers and further provides guidance for the methods required to map a QTL with a precision of 1 cM.

12. Claims 54, 107, 253, and 262 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aitman et al. in view of Manly et al. (cited as reference C75 in the Information Disclosure Statement filed 06 March 2006, Mammalian Genome Vol. 10, pages 327-334 (1999))

The claims are drawn to a method of measuring an expression quantitative trait locus (eQTL), a clinical quantitative trait locus (cQTL), and determining whether the gene assayed in the determination of the eQTL and the clinical trait are associated by determining if the eQTL and cQTL map to the same locus. The eQTL is limited to be an expression statistic for the gene that is the trait, i.e. the eQTL is a cis eQTL as limited in the claimed subject matter and discussed on page 95 of the specification. In some embodiments the claims are computer programs or

computers that execute the process. In some embodiments the mapping utilizes regression or interval mapping, or maximum likelihood analysis.

Aitman et al. shows in the abstract a method of genetically analyzing complex disorders such as diabetes by correlating a QTL for different traits of diabetes (insulin-mediated glucose uptake and catecholamine-mediated lipolysis) with mapping of the expression trait for the gene Cd36. Aitman et al. used spontaneously hypertensive rat (SHR) animals as the phenotype that was mapped by both eQTL and cQTL. Aitman et al. maps insulin-mediated glucose uptake and catecholamine-mediated lipolysis to a region near the microsatellite marker D4Bro1 on pages 76-77, which is a determination of a cQTL. Aitman et al. employs F2 crossed rats to map insulin-mediated glucose uptake and catecholamine-mediated lipolysis on page 79 to Cd36, which is a refinement of the mapping of the cQTL. Aitman et al. shows in figure 2 and the discussion on pages 77-78 analysis of expression level microarrays determined that expression of Cd36 correlates with SHR individuals relative to SHR.4 and BN individuals. Cd36 was then mapped to a region near the D4Bro1 site in figures 3 and page 78 using radiation hybrids to a precision of about 1cM with a Lod of 5.1 to 9.6 for the intervals measured. The mapping used a plurality of rat/hamster radiation hybrid cell lines to test a plurality of chromosomal locations for linkage to Cd36. Aitman et al. refined the mapping of Cd36 by use of linkage analysis on page 78 and figure 7 by testing linkage to chromosomal DNA of three rat strains. Page 79 and figure 7 show that Cd36 mutations correlate with the trait and that a normal and an affected strain differ by a duplication or deletion of the Cd36 gene. Figure 1 and column 1 on page 77 show that the phenotype in affected individuals has partial penetrance in affecting glucose uptake.

Aitman et al. discuss on page 82 the use of a computer program termed MAPMAKER, but Aitman et al. does not provide details of their genetic mapping calculations.

Manly et al. reviews computer software for use in QTL analysis. Manly et al. shows in the second column of page 327 that two methods widely used are least squares regression and maximum likelihood estimation. Manly et al. also discusses use of interval mapping on pages 327-328 for use in QTL mapping. Manly et al. review a number of programs used for QTL mapping, including MAPMAKER (used by Aitman et al.) on pages 329-330.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use a computer running the MAPMAKER program as shown in Aitman et al. because Manly et al. shows that MAPMAKER, as well as a number of other programs, are useful to map QTL markers. It would have been further obvious to use regression or maximum likelihood analysis, and additionally interval mapping because Manly et al. show that such analyses are useful to map QTL markers.

Response to Arguments

13. Applicant's arguments filed 30 April 2010 have been fully considered but they are not persuasive. The applicants state that Aitman et al. does not disclose the limitation added by amendment that the first quantitative trait analysis (an identification of an eQTL) comprises testing for linkages between the plurality of expression statistics for said gene G and a plurality of locations along a genetic map of the plurality of organisms. However as noted in the above rejections, Aitman et al. tests a plurality of locations in radiation hybrid cell lines and genomes of rat strains. The claim limitation only requires testing of a plurality of locations to determine

which location has the best linkage. The applicants further point to the statement in section 14 of the Office action mailed 02 November 2009 that recites:

Aitman et al. does not show mapping of a QTL with a precision of 1 cM, or determining whether a QTL maps to a plurality of positions in a genome.

The statement was intended to convey that Aitman et al. does not map a QTL simultaneously to a plurality of locations, not that Aitman et al. did not test a plurality of locations to map a QTL. The rejection has been rewritten to more clearly state what Aitman et al. does not show.

Conclusion

14. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/John S. Brusca/

Primary Examiner, Art Unit 1631

jsb